

Response to Questions from the Institute of Medicine

1. What evidence is there to conclude that there is or is not a threshold effect for cancer, heart disease, adverse reproductive effects or lung disease caused by exposure to tobacco or tobacco smoke, and what is the threshold level, if it exists.

This question may be relevant for people who start smoking and choose to use reduced harm products¹: Is there a chance of lower or negligible risk for disease? This question may also be relevant for people who already smoke and have the intention to switch to reduced harm products: Is there a chance for lower or even negligible risk by switching to already existing or to be developed less harmful cigarettes?

The question can be discussed based on epidemiological and mechanistic grounds, using the data available on the effects of smoking existing cigarette types and conceptual considerations.

^{current}
The gold standard for the determination of the existence of a threshold in the dose-response relationship of a disease is certainly epidemiology. However, the determination of thresholds requires a reasonable resolution of the dosimeter applied to the dose-response relationship under investigation. In terms of the cigarette smoke dose, epidemiology has been ^{primarily} ~~mainly~~ based on the number of cigarettes per day. Most epidemiological studies have used increments of 10 cigarettes per day [which is course relative to the current average consumption in the US of 19 cigarettes per day.] ^{or 10-15 years} ? Though the data is available for finer evaluations ^{has not been vocally reported.} Muscat Winden - ^{Reported self smoke survey} ^{10-15 years}

With the limitations in dose resolution ^{reliability} given, the dose-response relationship for lung cancer seems to be compatible with linearity in the lower-dose range (e.g., US DHHS 1982 and 1989; IARC, 1986;). The same holds true for other cancer types that are ^{also} related to cigarette smoking. For cardiovascular diseases, the dose-response relationship is relatively flat. In particular, the relative risk for ischemic heart disease was reported to be 1.78 for smoking 20 cigarettes per day (meta-analysis by Law et al., 1997). Extrapolating the data from this meta-analysis to the lower dose range with a super-linear convex dose-response relationship suggests a relatively high risk even ? for smoking few cigarettes per day. A similar pattern can be observed for the coronary heart disease mortality ratios comprised by the US DHHS (1983). For myocardial infarction, however, the US DHHS (1983) reported a supra-linear or concave dose-response relationship; however, the data did not suggest a threshold. For chronic bronchitis and emphysema, with the above-

¹ The term 'reduced harm products' as it is used here includes novel cigarette types as well as any kind of replacement therapy in combination with a reduced consumption of conventional cigarettes.

2 reported key element is related to imprec
generally conceivable. Non-linear dose-response approx.

Imprec
expos.

PM3006856764

1995). Oxidative modification of the low density lipoprotein is considered a critical step in atherosclerosis (McCall and Frei, 1999).

Most non-carcinogenic smoking-related health effects, such as the risk for chronic bronchitis or coronary heart disease, were also found to recover after smoking cessation (US DHHS, 1984 and 1989). For example, the abnormalities found in blood lipid profiles appear to reverse, at least in part, within weeks of smoking cessation (Stubbe et al., 1982). Also, the flow-mediated and endothelium-dependent peripheral arterial vasodilation, which is impaired by smoking, has been reported to be at least partly reversible after smoking cessation (Celermajer et al., 1993).

Conceptually, thresholds most likely exist for a number of mechanistic events in smoking-related diseases. However, practically these diseases develop in multiple stages (e.g., carcinogenesis) or parallel events (e.g., atherosclerosis and thrombosis) which makes it difficult to deduce thresholds for the overall disease outcome. In addition, these processes are triggered by exposure to a complex mixture of constituents, which may interact at various steps within the disease processes.

In summary, mechanistic considerations generally suggest that there are thresholds for smoking-related adverse health effects. However, thresholds or non-linear dose-response relationships have only rarely been determined in epidemiological studies on cigarette smoking-related diseases, which can be related to the complex exposure and the complex disease processes as well as to the ^{crude} rough dosimetry employed. Nevertheless, since all these effects are dose-dependent and the risks for many of them are reduced upon cessation of smoking, reduced exposure to the smoke constituents related to these effects are considered advantageous regardless of the presence of thresholds.

Dose response is trend

References

Celermajer, D.S., Sorensen, K.E., Georgakopoulos, D. et al.,
Cigarette smoking is associated with dose-related and potentially reversible impairment of
endothelium-dependent dilation in healthy young adults,
Circulation 88: 2149-2155 (1993).

Chemelevsky, D., Kellerer, A.M., Spiess, H., and Mays, C.W.,
A proportional hazards analysis of bone sarcoma rates in German radium-224 patients,
IN: The Radiobiology of Radium and Thorotrast (Gossner, W., and Gerber, G.B., eds.), Urban and
Schwarzenberg, Munich, 1986.

Eiserich, J.P., van der Vliet, A., Handelman, G.J., Halliwell B., and Cross, C.E.,

are they asking if there is a safe level of smoking? - yes
- have we answered it?
we currently do not have the tools to measure this (safe) - but we can approach from a risk reduction

PM3006856765

01-May-2000 HHM

Dietary antioxidants and cigarette smoke-induced biomolecular damage: a complex interaction, *Am. J. Clin. Nutr.* 62: 1490S-1500S (1995).

International Agency for Research on Cancer (IARC),
Tobacco Smoking, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 38, Lyon 1986.

Law, M.R., Morris, J.K., and Wald, N.J.,
Environmental tobacco smoke exposure and ischemic heart disease: an evaluation of the evidence, *Br. Med. J.* 315: 973-980 (1997).

McCall, M.R., and Frei, B.,
Can antioxidant vitamins materially reduce oxidative damage in humans?
Free Rad. Biol. Med. 26: 1034-1053 (1999).

Müller, L., and Kasper, P.,
Human biological relevance and the use of threshold-arguments in regulatory genotoxicity assessment: experience with pharmaceuticals, *Mutat. Res.* 464: 19-34 (2000).

Poirier, M.C., and Beland, F.A.,
DNA adduct measurement and tumor incidence during chronic carcinogen exposure in animal models: Implications for DNA adduct-based human cancer risk assessment, *Chem. Res. Toxicol.* 5: 749-755 (1992).

Purchase, I.,
Threshold methods should be used in risk assessment for genotoxic carcinogens, *IUTOX* newsletter July 1998, pp. 20-21.

Stellman, S.D.,
Cigarette yield and cancer risk: Evidence from case-control and prospective studies, in: *International Agency for Research on Cancer (IARC) Scientific Publications No. 74, Tobacco: A major international health hazard* (Zaridze, D.G., and Peto, R., eds.), p.187, Lyon, 1986.

Stubbe, I., Eskilsson, J., and Nilsson-Ehle, P.,
High-density lipoprotein concentrations increase after stopping smoking, *Br. Med. J.* 284: 1511-1513 (1982)

U.S. Department of Health and Human Services (DHHS),
The Health Consequences of Smoking for Women, a report of the Surgeon General, Rockville, MD, 1980.

U.S. Department of Health and Human Services (DHHS),
The Health Consequences of Smoking, Cancer, a report of the Surgeon General, Rockville, MD, 1982.

U.S. Department of Health and Human Services (DHHS),
The Health Consequences of Smoking, Cancer, a report of the Surgeon General, Rockville, MD, 1982.

PM3006856766

U.S. Department of Health and Human Services (DHHS),
The Health Consequences of Smoking, Cardiovascular Disease, a report of the Surgeon General,
Rockville, MD, 1983.

U.S. Department of Health and Human Services (DHHS),
The Health Consequences of Smoking, Chronic Obstructive Lung Disease, a report of the Surgeon
General, Rockville, MD, 1983.

U.S. Department of Health and Human Services (DHHS),
Reducing the Health Consequences of Smoking, 25 Years of Progress, a report of the Surgeon
General, Rockville, MD, 1989.

Zencik, H., and Bogdanffy, M.S.,
Harmonization of cancer and non-cancer risk assessment: moving beyond the NRC book,
The Toxicologist 54: 194 (2000).